

CLAIMS

1. Use of an immunomodulatory (IMC) or immunogenic (IC) composition and a $\gamma\delta$ T cell activator for the manufacture of a medicament, wherein said IMC or IC composition is for local
5 administration to a site of disease and said IMC or IC composition is used in combination with said $\gamma\delta$ T cell activator.
2. The use according to claim 1, wherein the IMC or IC is administered intravesically.
- 10 3. The use according to claim 1, wherein the IMC or IC is administered to the skin.
4. The use according to any one of the above claims, wherein the IMC or IC is administered intra-tumorally.
- 15 5. The use according to any one of the above claims, wherein said $\gamma\delta$ T cell activator is administered within 48 hours of administration of said IC or IMC.
6. The use of any one of the above claims, wherein the IMC comprises a compound capable of activating a $\gamma\delta$ T cell.
- 20 7. The use of any one of claims 1 to 5, wherein the IMC comprises a compound which is an agonist of a toll-like receptor (TLR).
8. The use of claim 7, wherein the toll-like receptor (TLR) is selected from the group consisting
25 of TLR2, TLR3, TLR4, TLR6, TLR7, TLR8, TLR9 and TLR10.
9. The use of any one of claims 1 to 5, wherein the IMC comprises a cytokine.
10. The use of claim 9, wherein the cytokine is selected from the group consisting of IL-2, IL-4,
30 IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, IL-18 and IL-21.
11. The use of claim 7, wherein the IMC comprises a compound which is an imidazoquinoline compound or analog or derivative thereof.
- 35 12. The use of claim 11, wherein said medicament is for the treatment of superficial basal cell carcinoma, HPV infection or malignant melanoma.

13. The use of claim 7, wherein the IMC comprises a CpG nucleic acid, or analog or derivative thereof.

5 14. The use of any one of claims 1 to 5, wherein said IC comprises a cancer antigen or a bacterial antigen.

15. The use of any one claims 1 to 5, wherein the IMC or IC comprises a Mycobacterium antigen.

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16. Use of a Mycobacterium antigen and a $\gamma\delta$ T cell activator for the manufacture of a medicament.

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17. The use of any one of claims 14 to 16, wherein said antigen is a purified or isolated polypeptide.

18. The use of any one of claims 14 to 16, wherein said IC or said Mycobacterium antigen comprises a killed or attenuated pathogen, microorganism or parasite.

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19. The use of claims 15 or 16, wherein said Mycobacterium antigen is an attenuated Mycobacterium strain.

20. The use of claim 19, wherein said attenuated Mycobacterium strain is an attenuated Mycobacterium bovis.

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21. The use according to any one of claims 15 to 19, wherein said Mycobacterium antigen is administered locally to a site of disease.

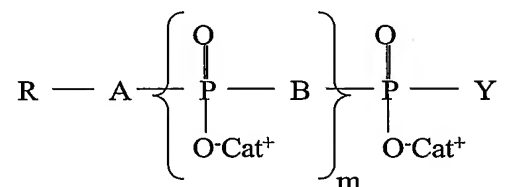
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22. The use according to claim 21, wherein said Mycobacterium antigen is administered topically to cutaneous, penile and perianal areas, or intraurethrally application to the urogenital tract.

23. The use according to claim 21, wherein said Mycobacterium antigen is administered intravesicularly into the bladder.

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24. The use according to any one of the above claims, wherein said $\gamma\delta$ T cell activator is administered within 48 hours of administration of said Mycobacterium antigen.
25. The use according to claim 23 wherein said Mycobacterium antigen is administered after a
5 transurethral resection.
26. The use according to claims 23 to 25, wherein said bladder cancer is a stage 0 bladder cancer.
- 10 27. The use according to claim 26, wherein said stage 0 bladder cancer is a non-invasive papillary carcinoma (TaT1) or a carcinoma in situ (CIS).
28. The use according to any one of the above claims, wherein said $\gamma\delta$ T cell activator is administered systemically.
- 15 29. The use according to any one of the above claims, wherein said $\gamma\delta$ T cell activator is administered intravenously, subcutaneously or intramuscularly.
30. The use according to any one of the above claims, wherein said $\gamma\delta$ T cell activator is an
20 aminobisphosphonate compound.
31. The use according to any one of the above claims, wherein said $\gamma\delta$ T cell activator is a selective $\gamma\delta$ T cell activator.
- 25 32. The use according to any one of the above claims, wherein said $\gamma\delta$ T cell activator is a compound of formula (I) :



Formula (I)

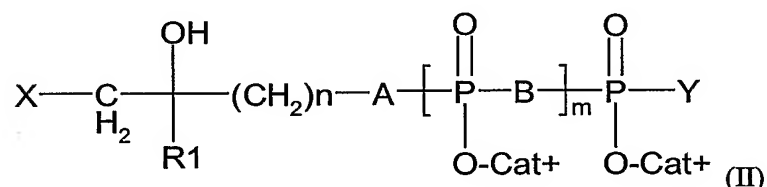
- wherein Cat^+ represents one (or several, identical or different) organic or mineral cation(s) (including proton);
- 30 m is an integer from 1 to 3;
- B is O, NH, or any group capable to be hydrolyzed;

Y = O⁻Cat⁺, a C₁-C₃ alkyl group, a group -A-R, or a radical selected from the group consisting of a nucleoside, an oligonucleotide, a nucleic acid, an amino acid, a peptide, a protein, a monosaccharide, an oligosaccharide, a polysaccharide, a fatty acid, a simple lipid, a complex lipid, a folic acid, a tetrahydrofolic acid, a phosphoric acid, an inositol, a vitamin, a co-enzyme, a flavonoid, an aldehyde, an epoxyde and a halohydrin;

A is O, NH, CHF, CF₂ or CH₂; and,

R is a linear, branched, or cyclic, aromatic or not, saturated or unsaturated, C₁-C₅₀ hydrocarbon group, optionally interrupted by at least one heteroatom, wherein said hydrocarbon group comprises an alkyl, an alkylenyl, or an alkynyl, preferably an alkyl or an alkylene, which can be substituted by one or several substituents selected from the group consisting of : an alkyl, an alkylenyl, an alkynyl, an epoxyalkyl, an aryl, a heterocycle, an alkoxy, an acyl, an alcohol, a carboxylic group (-COOH), an ester, an amine, an amino group (-NH₂), an amide (-CONH₂), an imine, a nitrile, an hydroxyl (-OH), a aldehyde group (-CHO), an halogen, an halogenoalkyl, a thiol (-SH), a thioalkyl, a sulfone, a sulfoxide, and a combination thereof.

33. The use according to claim 32, where said γδ T cell activator is a compound of formula (II):



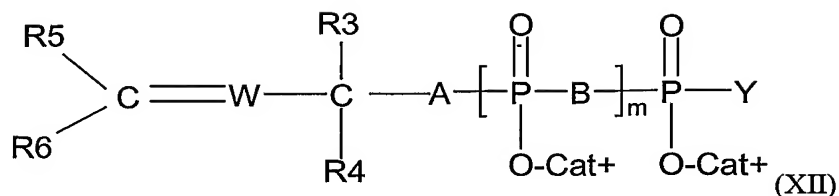
in which X is an halogen (preferably selected from I, Br and Cl), B is O or NH, m is an integer from 1 to 3, R1 is a methyl or ethyl group, Cat⁺ represents one (or several, identical or different) organic or mineral cation(s) (including the proton), and n is an integer from 2 to 20, A is O, NH, CHF, CF₂ or CH₂, and Y is O⁻Cat⁺, or a nucleoside.

34. The use according to claim 33, wherein the compound of formula (II) is BrHPP.

35. The use according to claim 33, wherein the compound of formula (II) is CBrHPP.

36. The use according to claim 32, wherein the compound of formula (II) is epoxPP.

37. The use according to any one of claims 1-32, where said γδ T cell activator is a compound of formula (XII):



in which R₃, R₄, and R₅, identical or different, are a hydrogen or (C₁-C₃)alkyl group, W is -CH- or -N-, R₆ is an (C₂-C₃)acyl, an aldehyde, an (C₁-C₃)alcohol, or an (C₂-C₃)ester, Cat⁺ represents one (or several, identical or different) organic or mineral cation(s) (including the proton), B is O or NH, m is an integer from 1 to 3, A is O, NH, CHF, CF₂ or CH₂, and Y is O⁻Cat⁺, or a nucleoside.

38. The use according to claim 37, wherein the compound of formula (XII) is HDMAPP.

39. The use according to claim 37, wherein the compound of formula (XII) is CHDMAPP.

40. The use according to any one of the above claims, wherein said medicament is for the treatment of a disease selected from the group consisting of a proliferative disorder, a carcinoma or a viral infection.

41. The use according to claim 40, wherein said disease is selected from the group consisting of a bladder cancer, a skin tumor or cancer, and an HPV infection.

42. A pharmaceutical composition comprising a Mycobacterium antigen and a $\gamma\delta$ T cell activator at an effective dose to treat a carcinoma or viral infection.

43. A kit comprising a pharmaceutical composition comprising an IC or IMC and a pharmaceutical composition comprising a $\gamma\delta$ T cell activator, said compositions at effective doses to treat a carcinoma or viral infection when used together in combination therapy and wherein the IC or IMC is provided in a form suitable for local administration to a site of disease.

44. The kit according to claim 43, wherein the IC or IMC is a Mycobacterium antigen.

45. The kit or pharmaceutical composition according to claims 42 or 44, wherein said Mycobacterium antigen is an attenuated Mycobacterium strain.

46. The kit or pharmaceutical composition according to claims 42 or 44, wherein said Mycobacterium antigen and said $\gamma\delta$ T cell activator are administered simultaneously.

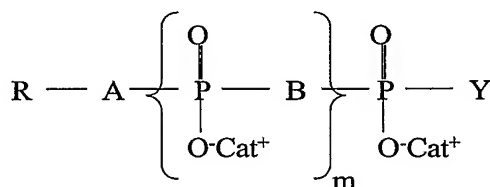
47. The kit or pharmaceutical composition according to claims 42 or 44, wherein said
5 Mycobacterium antigen and said $\gamma\delta$ T cell activator are administered separately.

48. The kit or pharmaceutical composition according to claim 46, wherein said Mycobacterium antigen and said $\gamma\delta$ T cell activator are administered by the same route.

10 49. The kit or pharmaceutical composition according to anyone of claims 42, or 44 to 48, wherein said Mycobacterium antigen and said $\gamma\delta$ T cell activator are administered by different routes.

50. The kit or pharmaceutical composition according to anyone of claims 42 or 44 to 49,
15 wherein said Mycobacterium antigen is administered intravesicularly into the bladder.

51. The kit or pharmaceutical composition according to anyone of claims 42 to 50, wherein said $\gamma\delta$ T cell activator is a compound of formula (I) :



Formula (I)

20 wherein Cat⁺ represents one (or several, identical or different) organic or mineral cation(s) (including proton);

m is an integer from 1 to 3;

B is O, NH, or any group capable to be hydrolyzed;

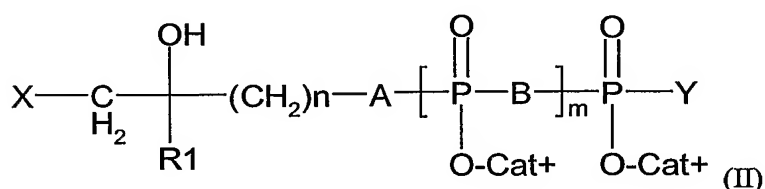
Y = O⁻Cat⁺, a C₁-C₃ alkyl group, a group -A-R, or a radical selected from the group consisting
25 of a nucleoside, an oligonucleotide, a nucleic acid, an amino acid, a peptide, a protein, a monosaccharide, an oligosaccharide, a polysaccharide, a fatty acid, a simple lipid, a complex lipid, a folic acid, a tetrahydrofolic acid, a phosphoric acid, an inositol, a vitamin, a co-enzyme, a flavonoid, an aldehyde, an epoxyde and a halohydrin;

A is O, NH, CHF, CF₂ or CH₂; and,

30 R is a linear, branched, or cyclic, aromatic or not, saturated or unsaturated, C₁-C₅₀ hydrocarbon group, optionally interrupted by at least one heteroatom, wherein said hydrocarbon group

- comprises an alkyl, an alkylenyl, or an alkynyl, preferably an alkyl or an alkylene, which can be substituted by one or several substituents selected from the group consisting of : an alkyl, an alkylenyl, an alkynyl, an epoxyalkyl, an aryl, an heterocycle, an alkoxy, an acyl, an alcohol, a carboxylic group (-COOH), an ester, an amine, an amino group (-NH₂), an amide (-CONH₂), an imine, a nitrile, an hydroxyl (-OH), a aldehyde group (-CHO), an halogen, an halogenoalkyl, a thiol (-SH), a thioalkyl, a sulfone, a sulfoxide, and a combination thereof.

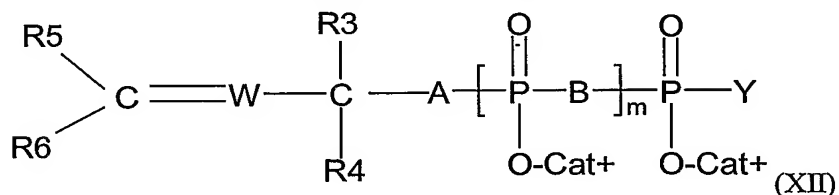
52. The kit or pharmaceutical composition according to claim 51, where said $\gamma\delta$ T cell activator is a compound of formula (II):



- in which X is an halogen (preferably selected from I, Br and Cl), B is O or NH, m is an integer from 1 to 3, R1 is a methyl or ethyl group, Cat⁺ represents one (or several, identical or different) organic or mineral cation(s) (including the proton), and n is an integer from 2 to 20, A is O, NH, CHF, CF₂ or CH₂, and Y is O⁻Cat⁺, or a nucleoside.

53. The kit or pharmaceutical composition according to claim 51 or 52, wherein the compound of formula (II) is selected from the group consisting of BrHPP, CBrHPP and epoxPP.

54. The kit or pharmaceutical composition according to anyone of claims 42 to 51, where said $\gamma\delta$ T cell activator is a compound of formula (XII):



- in which R₃, R₄, and R₅, identical or different, are a hydrogen or (C₁-C₃)alkyl group, W is -CH- or -N-, R₆ is an (C₂-C₃)acyl, an aldehyde, an (C₁-C₃)alcohol, or an (C₂-C₃)ester, Cat⁺ represents one (or several, identical or different) organic or mineral cation(s) (including the proton), B is O or NH, m is an integer from 1 to 3, A is O, NH, CHF, CF₂ or CH₂, and Y is O⁻Cat⁺, or a nucleoside.

55. The kit or pharmaceutical composition according to claim 54, wherein the compound of formula (XII) is HDMAPP or CHDMAPP.

56. A method for treating a carcinoma or viral infection in a patient, comprising administering
5 to a patient in need thereof an amount of a Mycobacterium antigen and a $\gamma\delta$ T cell activator effective to treat said carcinoma or viral infection.

57. A method for treating a disease comprising in a subject, comprising:

- (a) administering to said subject a $\gamma\delta$ T cell activator compound; and
- 10 (b) administering to a subject locally at a site of disease an immunomodulatory composition (IMC) or immunogenic composition (IC).